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SYNTHESIS, CRYSTAL STRUCTURE AND HERBICIDAL ACTIVITY OF A SERIES OF [1,2,4]TRIAZOLO[1,5-*a*]PYRIMIDINE-2-SULFONAMIDE COMPOUNDS

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Abstract – With the aim of obtaining efficient, safe and environmentally friendly green herbicide, a series of [1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide compounds (**8a**–**8f**) were synthesized by reacting 2-amino-5,7-(bis-substituted)-1,2,4-triazolo[1,5-*a*]pyrimidine (**4a** and **4b)** with 2-substituted-6-trifluoromethyl-benzenesulfonyl chloride (**7a**–**7c**). And their structures were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, FTIR, single-crystal X-ray diffraction, elemental analysis. Moreover, their herbicidal activities against six species of weeds were evaluated. Three target compounds such as **8a**, **8c** and **8e**, exhibited significant postemergence herbicidal activity against some common dicotyledons and monocotyledons under different concentrations. The structure and activity relationship is discussed based on the herbicidal performances of the compounds with different substituents. The investigation results indicated that the above structures could serve as lead compounds for the development of new herbicides.

INTRODUCTION

In recent years, the proposal of "green pesticide" aroused many researchers' interest in designing new type pesticides. "Green pesticide" could not only control the growth of harmful organisms and increase the output of grain, but also greatly reduce the harm to people's health and the environment.[1,2] The previous studies have indicated that the biological activity of some new developed pesticides is much higher than traditional ones to even hundreds or thousands of times. The acetolactate synthase (ALS)

inhibitor can block the synthesis of amino-acids to destroy the synthesis of proteins in the weeds, which is considered to be a new type of effective and safe herbicide.[3,4] As a typical ALS inhibitor, the triazolopyrimidine compounds were developed by bioisosterism, which exhibit good herbicidal activity and bright market prospects.[5-11]

The general structure of the triazolopyrimidine sulfonamide compounds are composed of three parts: benzene ring, bridging chain and heterocyclic ring. Firstly, according to the Levitt's principle, the introduction of electron-withdrawing groups to benzene ring on *ortho*-position is beneficial to enhance the herbicidal activity.[12,13] For instance, Syngenta Company has already developed several commercialized varieties of sulfonylurea herbicides such as triasulfuron, prosulfuron, in the structures of which, the chloroethoxy and trifluoropropyl group were introduced in the *ortho*-position of benzene ring to modify the compounds.[14,15] Secondly, the length and the substituent groups of the bridging chain could also affect biological activity of the triazolopyrimidine sulfonamide compounds.[16] The biological activity of the target compounds would be decreased with the introduction of methylene, oxygen atoms and etc. to the bridging chain, however, the presence of such groups could enhance their biodegradability. Some compounds with short bridging chains have good inhibiting activity on ALS. For example, the commercial product of Pyroxsulam and Penoxsulam with sulfonamido group as the linkage exhibit excellent herbicidal activity.[17-19] Last but not the least, the good candidates for the heterocyclic ring should consist of urea linkage, such as pyrimidine and triazine ring, and the substitution of which on 4- and/or 6-position by a short chain such as alkyl and alkoxy would show high herbicidal activity.[20-22]

Herein, we designed and synthesized six derivatives of [1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide, namely, 2-fluoro-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (**8a**), 2-fluoro-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide (**8b**), 2-(2,2-difluoroethoxy)-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (**8c**), 2-(2,2-difluoroethoxy)-*N*-(5,7-dimethyl[1,2,4]triazolo-[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (**8d**), 2-(tetrahydro-2-furanylmethoxy)-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (**8e**), and 2-(tetrahydro-2-furanylmethoxy)-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide (**8f**). As mentioned above, the following points are considered in the design of the six compounds: (1) As for the first structural part of benzene ring, the *ortho*-positions of the benzene ring in these six compounds were substituted, respectively, by different groups, such as trifluoromethyl, fluoro, 2,2-difluoroethoxy, and tetrahydro-2-furanylmethoxy. (2) As for the second structural part of bridging chain, the sulfonamido group was selected as the short bridging chain. (3) As for the third structural part of heterocyclic ring, two kinds of bis-substituted triazolopyrimidine were adopted considering their excellent biological activity exhibited in a lot of present herbicidal structures. These six compounds are

characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, FTIR and elemental analysis. The suitable single crystals of compounds **8a**, **8d** and **8e** were obtained to determine their absolute configuration by single-crystal X-ray diffraction. In addition, the herbicidal activities of these six compounds were evaluated. The primary screening test shows that all six compounds have fine biological activities on six species of weeds. And it is also encouraging to find that the compounds **8a**, **8c** and **8e** demonstrated good herbicidal activities in the further screening test, especially the herbicidal activity of compound **8a** is comparable with the commercial product of Penoxsulam (positive control).

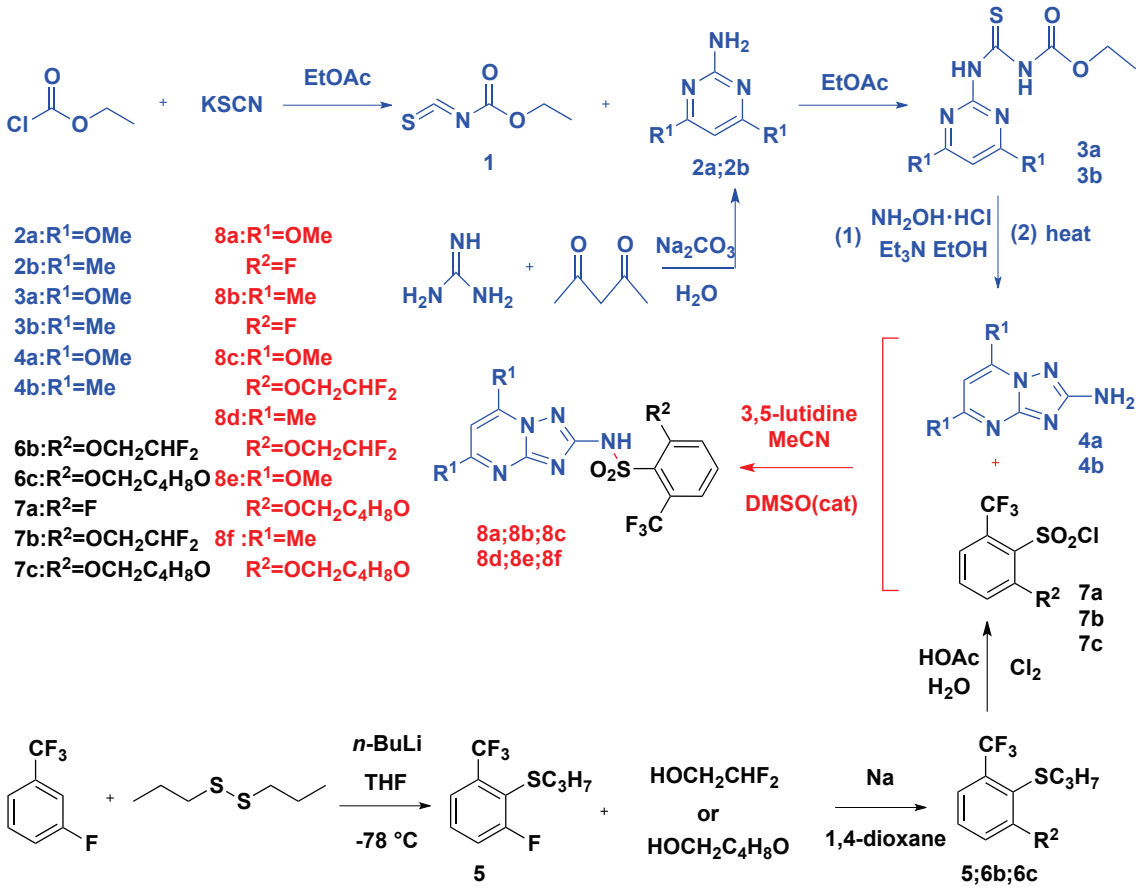
RESULTS AND DISCUSSION

Synthesis

The synthetic route of title compounds are given in Scheme 1. The key intermediate **4**[23] can be synthesized by a three-step synthetic route using the as-synthesized ethoxycarbonyl isothiocyanate **1** as the starting material. The compound **1** has irritant smell and is sensitive to water, which can be synthesized easily by reacting ethyl chloroformate with potassium thiocyanate in good yield and be directly used for the next reaction without separation. Therefore, the compound **3a** can be prepared by a one-pot method with adding the commercially available **2a** to the reaction solution of compound **1**, given about 84% yield. Subsequently, important intermediate **4a** was synthesized in 91.5% yield by heating **3a** with hydroxylamine in ethanol based on Tisler's cyclization reaction.[24] The compound **4b** was prepared in the same method as **4a** except that 2-amino-4,6-dimethylpyrimidine **2b** was synthesized in 69.5% yield by reported methods.[25]

The key intermediate **7** can be obtained by a three-step synthetic route using the commercially available 3-fluorobenzotrifluoride as the starting material. After lithiation and etherification reactions, the intermediate 2-fluoro-6-trifluoromethyl phenyl alkyl sulfide **5** was obtained in a yield of 66.5%. The intermediates **6b** and **6c** were prepared by reaction of 2,2-difluoroethanol and tetrahydrofurfuryl alcohol with **5** in the presence of metallic sodium as the alkali. The corresponding benzenesulfonyl chloride **7a**–**7c** can be achieved by ventilating Chlorine gas into the acetic acid aqueous solution of **5**, **6b** and **6c**. Taking into account the instability of the benzenesulfonyl chlorides **7a**–**7c**, they were used directly in the next condensation without any separation and purification. Finally, the title compounds **8a**–**8f** were prepared by condensation of intermediates **4a**,**b** with **7a**–**7c** in the presence of DMSO and 3,5-lutidine as the base and acetonitrile as the solvent.

The chemical structures of the synthetic sulfonamides **8a**–**8f** were confirmed by ^{1}H-NMR, ^{13}C-NMR and HRMS spectra data. Furthermore, the structures of compounds **8a**, **8d** and **8e** were verified by single-crystal X-ray diffraction analysis.



Scheme 1. Synthetic Procedure for the Target Compounds **8a**–**8f**

Crystal structures of compounds 8a, 8d and 8e

Single-crystal X-ray diffraction analysis are employed to determine the explicit structural information of these title compounds, considering that many N, O etc. hetero atoms and limited C and H in the structure gave limited information in NMR analysis. The single crystals of compounds **8a**, **8d** and **8e** were separated successfully from acetonitrile (Figure 1).

As shown in Figure 1, these three compounds are all consisted of triazolopyrimidine rings, benzene rings, and sulfonamido chains, in which the bond lengths and angles agreed well with the standard values (Table S2 in supporting information). The bond lengths within the triazolopyrimidine groups exhibited some degree of delocalization with the average lengths of 1.350 Å in **8a**, and 1.354 Å in **8d** and **8e**, and the N–N bond lengths are 1.374(3) and 1.377(3) Å in **8a**, 1.364(2) Å, and 1.409(4) Å in **8e,** which further confirms the delocalization of the triazolopyrimidine groups. In these compounds, the triazolopyrimidine rings and benzene rings are linked by the sulfonamido chains in the similar twisted modes with the dihedral angles of 75.5(1) and 78.9(1)° for **8a**, 72.5(1)° for **8d**, and 72.8(1)° for **8e**, respectively. In compounds **8a** and **8d**, the imide groups acted as the hydrogen bonds donor to the N atoms of the adjacent molecules, giving rise to the dimer structures (Table S2 in supporting information). All dimers exhibit a

8-membered hydrogen bonded ring with a unitary graph-set descriptor $N_1 = R^2_2(8)$.[26] However, in compound **8e**, the imide groups served as the hydrogen donor to the O atom of the tetrahydrofuran group of the same molecule to form the intramolecular hydrogen bond.

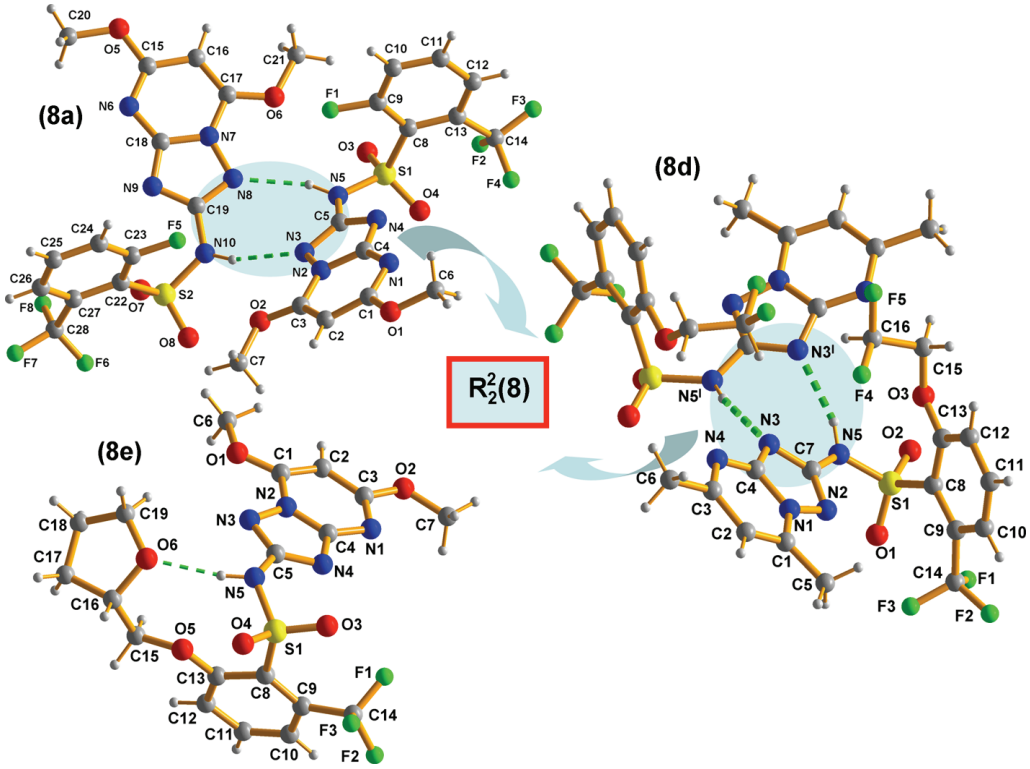


Figure 1. Crystal structures of compounds **8a**, **8d** and **8e**. Green dotted lines indicate the hydrogen bonds. Symmetric code in **8d**: I = –x, y, 0.5–z

Table 1. Inhibitory Effect of Compounds **8a–8f** on the Growth of Seed Roots and Shoots (Percent Inhibition, %)

compounds	dosage (mg/L)	CS		BC		EC		TA		SV		RS	
		root	shoot	root	shoot	root	shoot	root	shoot	root	shoot	root	shoot
8a	100	80	80	80	80	80	80	90	90	80	80	80	80
8b	100	80	80	80	80	80	80	80	80	50	50	80	80
8c	100	80	80	80	80	80	80	90	90	80	80	80	80
8d	100	80	80	80	80	80	80	50	50	50	50	80	80
8e	100	80	80	80	80	80	80	90	90	90	90	80	80
8f	100	80	80	80	80	80	80	90	90	80	80	80	80
Penoxsulam	100	80	80	80	80	80	80	90	90	80	80	80	80

Abbreviations: CS, *Cucumis sativus*; BC, *Brassica campestris*; EC, *Echinochloa crus-galli*; TA, *Triticum aestivum*; SV, *Sorghum vulgare pers*; RS, *Raphanus sativus*.

Growth Inhibition of Weed Roots and Shoots

The herbicidal activities of all target compounds were evaluated against pregerminate weed roots and shoots (*CS*, *BC*, and *EC*) and postemergence weed roots and shoots (*TA*, *SV*, and *RS*) in climatic camber. Penoxsulam was used as the positive control, and the results are shown in Table 1. The herbicidal activity evaluation indicated that all of the synthetic compounds showed "excellent" herbicidal activity against the test weeds that were etiolated followed by withering.

Herbicidal Activity in Greenhouse Conditions

The postemergence herbicidal activities of compounds **8a–8f** were evaluated against winter weeds (*BJ*, *PA*, *SM*, *AA*, *CA*, and *PF*) in the greenhouse environment, with Penoxsulam used as the positive control, and the results are shown in Table 2. The result manifests that compounds **8b**, **8d** and **8f** with methyl group on the heterocyclic ring (R^1=Me) show a weaker herbicidal efficiency than the ones **8a**, **8c** and **8e** substituted with methoxy group (R^1=OMe). It is observed that this series of compounds generally exhibits moderate activity at 150 g ai/ha dosage to broad leaf weeds *BJ* and *SM* but low activity in other instances. Compounds **8a**, **8c** and **8e** with the methoxy group show significant postemergence herbicidal activity against dicotyledonous weeds (*BJ*, *SM*, and *CA*) (≥80.0%) and monocotyledonous weeds (*PA*, *AA*, and *PF*) (≥70.0%).

Table 2. Herbicidal Activity of the Compounds **8a–8f** (Percent Inhibition, %)

compounds	dosage (g ai/ha)	Postemergence treatment					
		BJ	PA	SM	AA	CA	PF
8a	150	100	90	100	90	95	90
8b	150	100	0	100	0	65	0
8c	150	100	90	100	70	100	70
8d	150	100	0	100	0	25	0
8e	150	100	85	100	80	90	70
8f	150	100	0	100	0	0	0
Penoxsulam	150	100	80	100	85	80	70

Abbreviations: BJ, *Brassica juncea*; PA, *Poa annua L*; SM, *Stellaria media*; AA, *Alopecurus aequalis sobol*; CA, *Chenopodium album*; PF, *Polypogon fugax*.

Compounds **8a**, **8c** and **8e** with effective activities were selected for further herbicidal testing at lower dosages (Table 3). They exhibit better weeds control ability against dicotyledons (*AR* and *EP*) than monocotyledons (*DS*, *EC*, and *SV*), the inhibition ability of which are comparable with the positive

control Penoxsulam except for AT. Especially, compound **8a** shows excellent inhibition against monocotyledons *DS* and *SV* with an inhibitory percent up to 80% and 95% at a dosage of 150 g ai/ha, which is better than Penoxsulam. Meanwhile, compound **8c** also exerts effective inhibition to monocotyledons *DS* and *SV*. It was found that compound **8a**, **8c** displayed a broader spectrum of weed control than Penoxsulam even under low dosage with the *ortho*-position of benzene ring substituted with groups containing fluoro atoms (R^2=F, OCH_2CHF_2). These results enable these compounds to be potential candidates for further investigations as new herbicides.

Table 3. Further Herbicidal Testing of the Compounds **8a–8f** (Percent Inhibition, %)

compounds	dosage (g ai/ha)	Postemergence treatment					
		AT	DS	AR	EC	EP	SV
8a	37.5	50	30	100	95	100	80
	75	60	60	100	100	100	85
	150	85	80	100	100	100	95
8c	37.5	70	20	100	100	100	80
	75	85	30	100	100	100	85
	150	90	50	100	100	100	90
8e	37.5	60	0	100	90	100	20
	75	80	0	100	100	100	30
	150	90	0	100	100	100	60
Penoxsulam	37.5	90	0	100	100	100	30
	75	100	0	100	100	100	60
	150	100	20	100	100	100	80

Abbreviations: AT, *Abutilon theophrasti*; DS, *Digitaria sanguinalis*; AR, *Amaranthus retroflexus*; EC, *Echinochloa crus-galli*; EP, *Eclipta prostrate*; SV, *Setaira viridis*.

Table 4. Crop Selectivity of Compounds **8a–8f** (fresh weight reduction, %)

compounds	dosage (g ai/ha)	Postemergence treatment					
		maize	rice	cotton	soybean	rape	wheat
8a	150	30.94	32.82	-36.62	13.08	71.90	33.50
8c	150	10.32	3.94	52.87	48.21	87.20	1.20
8e	150	4.75	-4.46	37.26	24.38	61.50	8.20
Penoxsulam	150	-22.90	8.76	-12.32	100.00	67.90	25.00

Crop Selectivity

On the basis of the herbicidal activities mentioned above, some representative compounds **8a**, **8c** and **8e** were chosen for crop selectivity evaluation. As listed in Table 4, the results indicated that compounds **8a**, **8c** and **8e** demonstrated different crop selectivity to tested crops. Compound **8a** substituted with fluoro on benzene ring (R^2=F) was safe for cotton after postemergence application at a dosage of 150 g ai/ha, indicating that **8a** could be used in cotton fields to control weeds. Furthermore, **8c** with 2,2-difluoroethoxy substituent on benzene ring (R^2=OCH_2CHF_2) was safe for rice and wheat, whereas Penoxsulam was not selective for wheat (25% injury) at the concentration of 150 g ai/ha, suggesting that **8c** has a great potential as an effective herbicide for controlling weeds in rice and wheat fields. Meanwhile, **8e** with tetrahydro-2-furanylmethoxy substituent on benzene ring (R^2=$OCH_2C_4H_8O$) was safe for rice and maize, suggesting that **8e** might be as an effective herbicide in rice and maize fields.

In summary, six novel [1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide compounds were synthesized and identified as efficient ALS inhibitors for herbicidal activity. Most of the compounds displayed excellent inhibitory activity. Especially, when the heterocyclic ring is substituted with electron-donating groups (R^1=OMe), the compounds **8a**, **8c** and **8e** showed significant herbicidal activity and effective inhibition against broadleaf weeds and *Echinochloa crus-galli* at the rate of 37.5–150 g ai/ha. Moreover, when substituents containing fluoro atoms are adopted on the benzene ring (R^2=F, OCH_2CHF_2), compounds **8a**, **8c** displayed a broader spectrum of weed control than Penoxsulam even under low dosage. In addition, compounds **8a** was safe for cotton and **8c** was safe for rice and wheat, and **8e** was safe for maize, rice and wheat at the dosage of 150 g ai/ha. The results of this study also suggests that the [1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide is well worth further optimization. Further field trials and structure optimization of compounds **8a**, **8c** and **8e** are advancing.

EXPERIMENTAL

General

Chemicals and reagents were obtained from commercial sources. The tetrahydrofuran (THF) was dried by distillation over Na/benzophenone, and the other solvents were used as received without further purification. The purity of all the compounds were obtained from the test results of Shimadzu Liquid Chromatography LC-20A and Shimadzu Gas Chromatography GC-2010Plus. HPLC analysis condition: the chromatographic column was Welch Ultimate XB-C18 column (4.6 mm × 250 mm, 5μm); the detection wavelength was 254 nm; the mobile phase was methanol: 0.4% of phosphoric acid-water = 80 : 20 (V/V); and the flow rate was 0.8 mL/min for compounds **2b**, **3a**, **3b**, **4a**, **4b**, **5**, **6b**, **6c**, and **7a**–**7c**. While the mobile phase was acetonitrile: 0.4% of phosphoric acid-water = 70 : 30 (V/V); and the flow rate was 0.6 mL/min for compounds **8a**–**8f**. Melting points were determined by an MPA-100 automatic

melting point instrument and uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer Fourier transform infrared spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C-NMR spectra were obtained at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane (TMS) as the internal standard (TMS = 0.00 ppm). Chemical shifts (δ) are given in parts per million, and coupling constants (*J*) in hertz, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectrometry (HRMS) was recorded on a Bruker micrOTOF-QII. Elemental analysis were conducted on a varioMICRO CHN elemental analyzer.

Synthesis

Synthesis of Ethoxycarbonyl isothiocyanate (1): A solution of potassium thiocyanate (97.2 g, 1 mol) in EtOAc (600 mL) was heated up to 40 ºC, then ethyl chloroformate (106.3 g, 0.98 mol) was added slowly and the mixture was stirred at 40 ºC for 2 h. After that the solution was cooled to the room temperature and filtered to remove the potassium salt. The resultant solution was reserved for preparing compound **3**.

2-Amino-4,6-dimethoxypyrimidine (**2a**) is commercially available from Sigma Aldrich Chemical Company.

Synthesis of 2-Amino-4,6-dimethylpyrimidine (2b): A solution of guanidine nitrate (122.1 g, 1 mol) and 2,4-pentanedione (120.1 g, 1.2 mol) in water (800 mL) was stirred vigorously for 0.5 h at room temperature, and then sodium carbonate (74.2 g, 0.7 mol) was added. The resultant mixture was refluxed for 3 h, after that the mixture was cooled to the room temperature. The compound **2b** as the white precipitate was separated from the reaction solution, yield 85.6 g (69.5%); mp 153.8–154.5 ºC [lit.152–154 ºC][25]; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 1H, pyrimidine), 5.24 (s, 2H, NH_2), 2.29 (s, 6H, 2 × CH_3); *Anal*. Calcd for $C_6H_9N_3$: C 58.51, H 7.37, N 34.12. Found C 58.74, H 6.98, N 34.28.

Synthesis of *N*-(4,6-Dimethoxypyrimidine-2-yl)-*N'*-ethoxycarbonyl thiourea (3a): The compound **2a** (124.1 g, 0.8 mol) was added to the above mentioned solution of **1**, and then the mixture was stirred at 40 ºC for 6 h. The obtained mixture was cooled and filtered to achieve the solid which was then washed by 50 mL EtOAc. The compound **3a** was obtained as the yellow powder, yield 192.4 g (84.0%); mp 192.5–193.1 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H, NH), 11.52 (s, 1H, CONH), 6.02 (s, 1H, pyrimidine), 4.17 (q, *J* = 7.1 Hz, 2H, CH_2), 3.91 (s, 6H, 2 × CH_3), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3); *Anal*. Calcd for $C_{10}H_{14}N_4O_4S$: C 41.95, H 4.93, N 19.57. Found C 42.05, H 4.95, N 19.44.

Synthesis of *N*-(4,6-Dimethylpyrimidine-2-yl)-*N'*-ethoxycarbonyl thiourea (3b): The preparation of compound **3b** was similar to that of compound **3a**. The compound **3b** was obtained as the yellow powder, yield 176.4 g (86.7%); mp 177.6–178 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.30 (s, 1H, NH), 11.41 (s, 1H, CONH), 7.05 (s, 1H, pyrimidine), 4.17 (q, *J* = 7.1 Hz, 2H, CH_2), 2.40 (s, 6H, 2 × CH_3), 1.24 (t, *J* =

7.1 Hz, 3H, CH_3); *Anal*. Calcd for $C_{10}H_{14}N_4O_2S$: C 47.23, H 5.55, N 22.03. Found C 47.13, H 5.67, N 21.94.

Synthesis of 2-Amino-5,7-dimethoxy-1,2,4-triazolo[1,5-*a*]pyrimidine (4a): A solution of **3a** (114.5 g, 0.4 mol) and hydroxylamine hydrochloride (40.3 g, 0.58 mol) in EtOH (600 mL) was stirred vigorously for 0.5 h at 60 ºC, then triethylamine (58.7 g, 0.58 mol) was added dropwise into the mixture. The resultant mixture was refluxed for 5 h, then cooling to the room temperature. The white solid product of **4a** was collected by filtration and washed using 200 mL water, yield 71.4 g (91.5%); mp 275.6–277.5 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.06 (s, 1H, pyrimidine), 5.97 (s, 2H, NH_2), 4.06 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); *Anal*. Calcd for $C_7H_9N_5O_2$: C 43.08, H 4.65, N 35.88. Found C 42.91, H 4.47, N 36.21.

Synthesis of 2-Amino-5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (4b): The preparation of compound **4b** was similar to that of compound **4a**. The compound **4b** was obtained as the grey powder, yield 60.1 g (92.1%); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.82 (s, 1H, pyrimidine), 6.23 (s, 2H, NH_2), 2.55 (s, 3H, CH_3), 2.45 (s, 3H, CH_3); *Anal*. Calcd for $C_7H_9N_5$: C 51.52, H 5.56, N 42.92. Found C 51.64, H 5.52, N 42.84.

Synthesis of 2-Fluoro-6-trifluoromethylphenyl alkyl sulfides (5): A solution of 3-fluorobenzotrifluoride (82 g, 0.5 mol) in THF (320 mL) was cooled to -78 ºC with dry ice-acetone bath, then the reactor was filled and kept under a N_2 atmosphere. *N*-Butyllithium (200 mL, 0.5 mol) was added dropwise and the mixture was stirred at -70 ºC for 0.5 h, then dipropyl disulfide (75.1 g, 0.5 mol) was added slowly and kept stirring at -70 ºC for 1 h. After that an aqueous solution of NaCl (100 mL, 10%) was added to the reactor, then the pH value of the solution was adjusted to 3 with concentrated hydrochloric acid. The organic layer was washed with water and dried with anhydrous sodium sulfate, and then the solvent was removed by rotary evaporator. A yellow transparent liquid of compound **5** was obtained with 79.2 g (66.5%) yield; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.8 Hz, 1H, 5-phenyl-H), 7.38 (td, J = 8.0, 5.6 Hz, 1H, 3-phenyl-H), 7.27 (t, J = 8.3 Hz, 1H, 4-phenyl-H), 2.88 (t, J = 7.4 Hz, 2H, SCH_2), 1.63–1.53 (m, 2H, CH_2), 0.98 (t, J = 7.3 Hz, 3H, CH_3); *Anal*. Calcd for $C_{10}H_{10}F_4S$: C 50.41, H 4.23. Found C 50.11, H 4.10.

Synthesis of 2-(Tetrahydro-2-furanylmethoxy)-6-trifluoromethylphenyl alkyl sulfides (6c): To a solution of metallic sodium (34.5 g, 1.5 mol) in 1,4-dioxane (600 mL), tetrahydrofurfuryl alcohol (122.6 g, 1.2 mol) was added dropwise, and the resultant mixture was kept stirring at room temperature for 1 h. The mixture was heated to reflux, and compound **5** (238.2 g, 1 mol) was added, then the resultant mixture was kept refluxing for 2 h. After that an aqueous solution of NaCl (400 mL, 10%) was added to the reactor, then the pH value of the solution was adjusted to 7 with concentrated hydrochloric acid. The organic layer was washed with water and dried with anhydrous sodium sulfate, and then the solvent was removed by rotary evaporator. A yellow liquid of compound **6c** was obtained, yield 225.2 g (70.3%);

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 2H, 3 and 5-phenyl-H), 7.08 (t, *J* = 12.0 Hz, 1H, 4-phenyl-H), 4.37 (m, 1H, tetrahydrofurfuryl-CH), 4.08 (d, *J* = 4.8 Hz, 2H, OCH_2), 4.02–3.80 (m, 2H, 5-tetrahydrofurfuryl-CH_2), 2.89 (t, *J* = 7.4 Hz, 2H, SCH_2), 2.12 (dt, *J* = 14.2, 6.1 Hz, 2H, 4-tetrahydrofurfuryl-CH_2), 2.01–1.87 (m, 2H, 3-tetrahydrofurfuryl-CH_2), 1.54 (m, 2H, CH_2), 0.97 (t, *J* = 7.3 Hz, 3H, CH_3); *Anal*. Calcd for $C_{15}H_{19}F_3O_2S$: C 56.24, H 5.98. Found C 55.89, H 5.86.

Synthesis of 2-(2,2-Difluoroethoxy)-6-trifluoromethylphenyl alkyl sulfides (6b): The preparation of compound **6b** was similar to that of compound **6c**. The compound **6b** was obtained as the yellow transparent liquid, yield 195.5 g (65.1%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44–7.33 (m, 2H, 3 and 5-phenyl-H), 7.10–7.01 (m, 1H, 4-phenyl-H), 6.20 (tt, *J* = 55.0, 4.1 Hz, 1H, CHF_2), 4.28 (td, *J* = 13.0, 4.1 Hz, 2H, OCH_2), 2.85 (t, *J* = 7.4 Hz, 2H, SCH_2), 1.59–1.48 (m, 2H, CH_2), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3); *Anal*. Calcd for $C_{12}H_{13}F_5OS$: C 48.00, H 4.36. Found C 47.84, H 4.23.

Synthesis of 2-(Tetrahydro-2-furanylmethoxy)-6-trifluoromethylbenzenesulfonyl chloride (7c): Chlorine gas was ventilated slowly into a solution of **6c** (160.2 g, 0.5 mol) in HOAc (400 mL) and water (100 mL) until a clear solution was obtained. The resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic solution was washed with saturated sodium bicarbonate aqueous solution (3 × 300 mL), and then the solvent was removed by rotary evaporator. The obtained liquid was reserved for preparing compound **8a**–**8f**.

Compounds **7a** and **7b** were prepared by following the same procedure for **7c**.

Synthesis of 2-Fluoro-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide (8e): The compound **4a** (6 g, 0.03 mol), catalytic amount of DMSO and 3,5-lutidine (9.6 g, 0.09 mol) were dissolved in MeCN (15 mL), and then **7c** (10.3 g, 0.03 mol) was added slowly with stirring at 35 ºC and keeping for 1 h. The reaction system was heated to 45 ºC and kept that until the complete conversion monitoring by HPLC. Then the resultant mixture was slowly added into 10% sulfuric acid aqueous solution (100 mL). After filtering, the residue was purified by recrystallizing from MeCN to afford white solid, yield 13.5 g (89.6%); mp 212.6–214.6 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.74 (s, 1H, NH), 7.75 (t, *J* = 8.1 Hz, 1H, 4-phenyl-H), 7.59 (dd, *J* = 41.8, 7.9 Hz, 2H, 3 and 5-phenyl-H), 6.25 (s, 1H, pyrimidine), 4.34 (td, *J* = 10.8, 3.7 Hz, 2H, OCH_2), 4.12–4.04 (m, 4H, OCH_3 and tetrahydrofurfuryl-CH), 3.89 (s, 3H, OCH_3), 3.78 (ddd, *J* = 59.1, 14.7, 6.9 Hz, 2H, 5-tetrahydrofurfuryl-CH_2), 2.07–1.94 (m, 1H, 4-tetrahydrofurfuryl-CH), 1.94–1.77 (m, 2H, 3-tetrahydrofurfuryl-CH_2), 1.75–1.64 (m, 1H, 4-tetrahydrofurfuryl-CH); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 158.51, 157.78, 148.67, 144.32, 139.86, 134.83, 127.61, 124.52, 120.58, 76.87, 72.68, 68.27, 57.70, 56.35, 27.67, 25.63; IR (KBr cm^{-1}): *ν* 3100, 2948, 1573, 1309, 1104, 805, 569; *Anal*. Calcd for $C_{19}H_{20}F_3N_5O_6S$: C 45.33, H 4.00, N 13.91; found C 45.22, H 4.05, N 13.54; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{20}F_3N_5O_6S$: 503.1086. Found 503.0784.

The compounds **8a**–**8d** and **8f** were prepared by following the same procedure as that for **8e**.

Synthesis of 2-Fluoro-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonmide (8a): White solid; Yield 11.2 g (88.5%); mp 205.1–207.3 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1H, NH), 7.94–7.83 (m, 2H, 3 and 5-phenyl-H), 7.83–7.70 (m, 1H, 4-phenyl-H), 6.28 (s, 1H, pyrimidine), 4.09 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 168.08, 160.93, 158.39, 158.17, 157.09, 135.72, 129.45, 124.78, 124.19, 122.73, 80.28, 58.71, 55.06; IR (KBr cm^{-1}): ν 3112, 2957, 1574, 1312, 1172, 1098, 806, 568; *Anal*. Calcd for $C_{14}H_{11}F_4N_5O_4S$: C 39.91, H 2.63, N 16.62; found C 39.57, H 2.55, N 16.39; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{11}F_4N_5O_4S$: 421.0468. Found 421.0220.

Synthesis of 2-Fluoro-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide (8b): White solid; Yield 9.6 g (82.3%); mp 265.8–266.1 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.71 (s, 1H, NH), 7.89–7.81 (m, 2H, 3 and 5-phenyl-H), 7.78–7.67 (m, 1H, 4-phenyl-H), 7.06 (s, 1H, pyrimidine), 2.48 (s, 3H, CH_3), 2.47 (s, 3H, CH_3); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 164.62, 161.27, 158.73, 147.00, 135.74, 129.54, 124.52, 124.22, 122.69, 111.36, 24.71, 16.65; IR (KBr cm^{-1}): ν 3095, 2915, 1560, 1312, 1185, 1096, 808, 562; *Anal*. Calcd for $C_{14}H_{11}F_4N_5O_2S$: C 43.19, H 2.85, N 17.99; found C 42.81, H 2.75, N 17.53; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{11}F_4N_5O_2S$: 389.0570. Found 389.0343.

Synthesis of 2-(2,2-Difluoroethoxy)-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (8c)[24]: White solid; Yield 12.3 g (84.9%); mp 203–204 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H, NH), 7.78 (t, J = 8.2 Hz, 1H, 4-phenyl-H), 7.64 (dd, J = 14.9, 8.0 Hz, 2H, 3 and 5-phenyl-H), 6.52 (tt, J = 54.9, 3.9 Hz, 1H, CHF_2), 6.25 (s, 1H, pyrimidine), 4.51 (td, J = 13.9, 4.0 Hz, 2H, CH_2), 4.08 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 167.89, 158.54, 157.02, 156.69, 154.79, 134.69, 129.71, 128.65, 121.87, 121.47, 120.43, 114.58, 79.94, 69.08, 58.63, 54.96; IR (KBr cm^{-1}): ν 3108, 2957, 1563, 1307, 1176, 1103, 801, 578; *Anal*. Calcd for $C_{16}H_{14}F_4N_5O_5S$: C 39.76, H 2.92, N 14.49; found C 39.60, H 2.85, N 14.39; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{14}F_4N_5O_5S$: 483.0636. Found 483.0351.

Synthesis of 2-(2,2-Difluoroethoxy)-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (8d): Yellowish solid; Yield 11.3 g (83.3%); mp 245.8–247.5 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H, NH), 7.77 (t, J = 8.2 Hz, 1H, 4-phenyl-H), 7.63 (d, J = 8.2 Hz, 2H, 3 and 5-phenyl-H), 7.03 (s, 1H, pyrimidine), 6.72–6.36 (m, 1H, CHF_2), 4.50 (td, J = 13.8, 3.9 Hz, 2H, CH_2), 2.47 (s, 6H, 2 × CH_3); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 164.22, 159.20, 156.88, 146.67, 134.76, 130.18, 121.32, 120.40, 116.98, 114.60, 112.22, 110.84, 69.10, 24.70, 16.56; IR (KBr cm^{-1}): ν 3113, 2937, 1559, 1305, 1179, 1098, 793, 571; *Anal*. Calcd for $C_{16}H_{14}F_4N_5O_3S$: C 42.57, H 3.13, N 15.52; found C 42.40, H 2.93, N 15.31; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{14}F_4N_5O_3S$: 451.0738. Found

451.0460.

Synthesis of 2-(Tetrahydro-2-furanylmethoxy)-*N*-(5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (8f): White solid; Yield 12.2 g (85.9%); mp 184.8–186.3 ºC; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H, NH), 7.74 (t, J = 8.1 Hz, 1H, 4-phenyl-H), 7.58 (dd, J = 20.5, 8.0 Hz, 2H, 3 and 5-phenyl-H), 7.04 (s, 1H, pyrimidine), 4.43–4.30 (m, 2H, OCH_2), 3.95 (ddd, J = 21.2, 12.9, 7.6 Hz, 1H, tetrahydrofurfuryl-CH), 3.74 (dd, J = 14.6, 6.9 Hz, 2H, 5-tetrahydrofurfuryl-CH_2), 2.50 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.09–1.97 (m, 1H, 4-tetrahydrofurfuryl-CH), 1.94–1.79 (m, 2H, 3-tetrahydrofurfuryl-CH_2), 1.74–1.63 (m, 1H, 4-tetrahydrofurfuryl-CH); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 164.36, 159.23, 157.80, 154.18, 146.74, 134.75, 120.41, 110.94, 76.89, 72.78, 68.32, 27.64, 25.69, 24.71, 16.54; IR (KBr cm^{-1}): ν 3100, 2933, 1560, 1309, 1176, 1100, 803, 563; *Anal*. Calcd for $C_{19}H_{20}F_3N_5O_4S$: C 48.40, H 4.28, N 14.85; found C 48.33, H 4.17, N 14.59; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{20}F_3N_5O_4S$: 471.1188. Found 471.0941.

X-Ray Diffraction

The suitable crystals for X-ray single-crystal diffraction of compounds **8a**, **8d** and **8e** were obtained by recrystallizing them from MeCN. All measurements were performed at 293 K on an Oxford Xcalibur Gemini Ultra diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Empirical absorption corrections on the basis of equivalent reflections were applied. The structures of them were solved by direct methods and refined by full-matrix least-squares methods on F^2 using SHELXS-97 crystallographic software package.[27] Crystal parameters, data collection and refinement results for compounds **8a**, **8d** and **8e** are summarized in Table S1. And the selected bond lengths and angles are listed in Table S2, (see the Supporting Information). Crystallography data have been deposited to the Cambridge Crystallography Data Centre with deposition numbers of 1435072–1435074 for compounds **8a**, **8d** and **8e**.

Inhibitory Effect of Compounds 8a–8f on the Growth of Seed Roots and Shoots

Test compounds were formulated as 100 mg/L emulsified concentrates by using DMF as solvent and 1% Tween-80 as emulsification reagent. The stock solutions were diluted with water to the required concentration. *Cucumis sativus* (CS), *Brassica campestris* (BC), *Echinochloa crus-galli* (EC) and then *Triticum aestivum* (TA), *Sorghum vulgare pers* (SV), *Raphanus sativus* (RS) were accelerating germination soaked in distilled water for 4 h before being placed on a filter paper in a 9 cm Petri plate to which 9 mL of inhibitor solution had been added in advance and grown at 28 ºC in climatic camber, 75% relative humidity, and 16 h in the light and 8 h in the dark alternatively for 7 days, and the growth inhibitory rate related to untreated control was determined. The commercial herbicide Penoxsulam was used as the positive control. The results of these tests are presented in Table 1.

Screening in Greenhouse Conditions

The herbicidal activities of the title compounds **8a**–**8f** against winter weeds such as *Brassica juncea* (BJ), *Poa annua L* (PA), *Stellaria media* (SM), *Alopecurus aequalis sobol* (AA), *Chenopodium album* (CA), and *Polypogon fugax* (PF) were evaluated at 150 g ai/ha (Table 2). The target compounds **8a**, **8c** and **8e** were then selected for further test against summer weeds such as *Abutilon theophrasti* (AT), *Digitaria sanguinalis* (DS), *Amaranthus retroflexus* (AR), *Echinochloa crus-galli* (EC), *Eclipta prostrate* (EP) and *Setaira faberii* (SF) were evaluated at 37.5, 75 and 150 g ai/ha. Weed seeds were planted in 7.5 cm diameter plastic boxes containing three quarters of artificial mixed soil (vegetable soil : nursery substrate = 1 : 2, V/V), covering soil is 0.2 cm, At postemergence, the different concentrations inhibitor solution of the chemicals tested was applied to the foliage of plants grown at 3-leaf stage with a sprayer (3WPSH-700E), and grown in greenhouse 25 days. Assessments were made of % herbicidal effects, and test samples were given a score between 0 and 100, with 100 as complete control of the target and 0 as no effect. Penoxsulam was included in the test as a positive control compound. The results of these tests are presented in Table 3.

Crop Selectivity

The conventional maize, rice, cotton, soybean, rape and wheat were planted separately in 12 cm diameter plastic boxes containing selected soil and grown in a greenhouse at 20–25 °C. After the plants had reached the 4-5-leaf stage, inhibitor solution were spraying at the dosage of 150 g ai/ha. The visual injury and growth rate of the individual plants were observed at regular intervals. The fresh weights were determined 15 days later, and the percentage inhibition relative to the controls was calculated. Penoxsulam was selected as a positive control. The final results of crop safety were determined at Table 4.

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